EXCITOTOXINS
— DANGEROUS FOOD ADDITIVES —

Almost all processed foods contain powerful excitotoxins, such as MSG and aspartame, which are implicated in causing a variety of neurological disorders.

Part 1 of 2

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EXCITOTOXINS, NEURODEGENERATION AND NEURODEVELOPMENT

A growing number of clinicians and basic scientists are convinced that a group of compounds called "excitotoxins" play a critical role in the development of several neurological disorders, including migraines, seizures, infections, abnormal neural development, certain endocrine disorders, neuropsychiatric disorders, learning disorders in children, AIDS dementia, episodic violence, lyme borreliosis, hepatic encephalopathy, specific types of obesity, and especially the neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS), Parkinson's disease, Alzheimer's disease, Huntington's disease and olivopontocerebellar degeneration.[1]

An enormous amount of both clinical and experimental evidence has accumulated over the past decade, supporting this basic premise.[2] Yet, the FDA still refuses to recognise the immediate and long-term danger to the public caused by the practice of allowing various excitotoxins to be added to the food supply—excitotoxins such as MSG (monosodium glutamate), hydrolysed vegetable protein and aspartame. The amount of these neurotoxins added to our food has increased enormously since their introduction. For example, since 1948, the amount of MSG added to foods has doubled every decade. By 1972, 262,000 metric tons were being added to foods. Over 800 million pounds of aspartame have been consumed in various products since it was approved. Ironically, these food additives have nothing to do with preserving food or protecting its integrity; they are all used to alter the taste of food. MSG, hydrolysed vegetable protein and natural flavouring are used to enhance the taste of food, while aspartame is an artificial sweetener.

These toxins (excitotoxins) are not present in just a few foods, but, rather, in almost all processed foods. In many cases they are being added in disguised forms, such as natural flavouring, spices, yeast extract, textured protein, soy protein extract, etc. Experimentally, we know that when subtoxic levels of excitotoxins are given to animals in divided doses, the animals experience full toxicity, i.e., the excitotoxins are synergistic. Also, liquid forms of excitotoxins, as found in soups, gravies and diet soft drinks, are more toxic than that added to solid foods; this is because they are more rapidly absorbed and reach higher levels in the blood.

So, what are excitotoxins? These are substances, usually acidic amino acids, that react with specialised receptors in the brain in such a way as to lead to destruction of certain types of neurons. Glutamate is one of the more commonly known excitotoxins. MSG is the sodium salt of glutamate. This amino acid is a normal neurotransmitter in the brain. In fact, it is the neurotransmitter most commonly used by the brain. Defenders of MSG and aspartame usually ask how a substance that is used normally by the brain could cause harm. It is because glutamate, as a neurotransmitter, exists in the extracellular fluid only in very, very small concentrations—no more than 8 to 12 μM [micromoles/litre]. When the concentration of this transmitter rises above this level, the neurons begin to fire abnormally. At higher concentrations, the cells undergo a specialised process of delayed cell death known as "excitotoxicity"; that is, they are excited to death.

It should also be appreciated that the effects of excitotoxin food additives generally are not dramatic. Some individuals may be especially sensitive and develop severe symptoms and even die suddenly from cardiac irritability, but in most instances the effects are subtle and develop over a long period of time. While the food additives MSG and aspartame are probably not direct causes of the neurodegenerative diseases such as Alzheimer's dementia, Parkinson's disease or ALS, they may well precipitate these disorders and certainly worsen their pathology—as we shall see. It may be that many people with a propensity

for developing one of these diseases would never develop a full-blown disorder if not for their exposure to high levels of food-borne excitotoxin additives. Some might only have had a very mild form of the disease, if not for the exposure. Likewise, food-borne excitotoxins may be harmful to those suffering from strokes, head injury and HIV infection, and certainly should not be used in a hospital setting.

THE DISCOVERY OF EXCITOTOXINS

In 1957, two opthalmology residents, Lucas and Newhouse, were conducting an experiment on mice to study a particular eye disorder.[3] During the course of this experiment, they fed newborn mice MSG and discovered that all demonstrated widespread destruction of the inner nerve layer of the retina. Similar destruction was also seen in adult mice, but was not as severe as in the newborns. The results of their experiment were published in the *Archives of Opthalmology* and soon forgotten. For 10 years prior to this report, large amounts of MSG were being added not only to adult foods but also to baby foods, in doses equal to those given to the experimental animals.

When excitotoxin taste-enhancers are added together, they become much more toxic than if taken individually.

Then, in 1969, Dr John Olney, a neuroscientist and neuropathologist working out of the Department of Psychiatry at Washington University in St Louis, repeated Lucas and Newhouse's experiment.[4] His lab assistant noticed that the newborn of MSG-exposed mice were grossly obese and short in stature. Further examination also demonstrated hypoplastic organs, including pituitary, thyroid and adrenal, as well as reproductive dysfunction. Physiologically, they demonstrated multiple endocrine deficiencies, including of TSH, growth hormone, LH, FSH and ACTH. When Dr Olney examined the animals' brains, he discovered discrete lesions of the arcuate nucleus as well as less severe destruction of other hypothalamic nuclei.

Since this early observation, monosodium glutamate and other excitatory substances have become standard tools in studying the function of the hypothalamus. Recent studies showed that glutamate is the most important neurotransmitter in the hypothalamus.[5] Later studies indicated that the damage by monosodium glutamate was much more widespread, affecting the hippocampus, circumventricular organs, locus ceruleus, amygdala, limbic system, subthalamus and striatum.[6] More recent molecular studies disclosed the mechanism of this destruction in some detail.[7]

Early on, it was observed that when neurons *in vitro* were exposed to glutamate and then washed clean, the cells appeared perfectly normal for approximately an hour, at which time they rapidly underwent cell death. It was discovered that when calcium was removed from the medium, the cells continued to survive.

Subsequent studies have shown that glutamate and other excitatory amino acids attach to a specialised family of receptors (NMDA, kainate, AMPA and metabotrophic) which in turn, either directly or indirectly, opens the calcium channel on the neuron cell membrane, allowing calcium to flood into the cell. If unchecked, this calcium will trigger a cascade of reactions, including free radical generation, eicosanoid production and lipid peroxidation, which will destroy the cell. With this calcium-triggered stimulation, the neuron becomes very excited, firing its impulses repetitively until the point of cell death, hence the name "excitotoxin". The activation of the calcium channel via the NMDA-type receptors also involves other membrane receptors such as the zinc, magnesium, phencyclidine and glycine receptors.

In many disorders connected to excitotoxicity, the source of the glutamate and aspartate is endogenous. We know that when brain cells are injured, they release large amounts of glutamate from surrounding astrocytes, and this glutamate can further damage surrounding normal neuronal cells. This appears to be the case in strokes, seizures and brain trauma. But, food-borne excitotoxins can add significantly to this accumulation of toxins.

COUNTERING THE FDA'S SPIN ON MSG SAFETY

In July 1995, the Federation of American Societies for Experimental Biology (FASEB) conducted a definitive study for the US Food and Drug Administration (FDA) on the question of safety of MSG.[8] The FDA wrote a very deceptive summary of the report in which it implied that, except possibly for asthma patients, MSG was found to be safe by the FASEB reviewers. But, in fact, that is not what the report said at all.

I summarised, in detail, my criticism of this widely reported FDA deception in the revised paperback edition of my book, *Excitotoxins: The Taste That Kills*, by analysing exactly what the report said and failed to say.[9] For example, it never said that MSG did not aggravate neurodegenerative diseases. What it said was, there were no studies indicating such a link; specifically, that no one has conducted any studies, positive or negative, to see if there is a link. A vital difference.

Unfortunately for the consumer, the corporate food processors not only continue to add MSG to our foods but go to great lengths to disguise these harmful additives. For example, they use such names as "hydrolysed vegetable protein", "vegetable protein", "textured protein", "hydrolysed plant protein", "soy protein extract", "caseinate",

"yeast extract" and "natural flavouring". We know experimentally that when these excitotoxin taste-enhancers are added together, they become much more toxic than is seen individually.[10] In fact, excitotoxins in subtoxic concentrations can be fully toxic to specialised brain cells when used in combination. Frequently on supermarket shelves I see processed foods, especially frozen or diet foods, that contain two, three or even four types of excitotoxins.

We also know, as stated, that excitotoxins in liquid forms are much more toxic than solid forms because they are rapidly absorbed and attain high concentration in the blood. This means that many of the commercial soups, sauces and gravies containing MSG are very dangerous to nervous system health, and should especially be avoided by those who have one of the above-mentioned disorders or who are at a high risk of developing one of them. They should also be avoided by cancer patients and those at high risk for cancer, because of the associated generation of free radicals and lipid peroxidation.[11]

In the case of amyotrophic lateral sclerosis (ALS), we know that consumption of red meats, and especially MSG itself, can significantly elevate blood glutamate to levels much higher than seen in the normal population.[12] Similar studies, as far as I am aware, have not been conducted in patients with Alzheimer's or Parkinson's disease. But, as a general rule, I would certainly suggest that persons with either of these diseases avoid MSG-containing foods as well as red meats, cheeses and puréed tomatoes, all of which are known to have higher levels of glutamate.

It must be remembered that it is the glutamate molecule that is toxic in monosodium glutamate. Glutamate is a naturally occurring amino acid found in varying concentrations in many foods. Defenders of MSG safety allude to this fact in their defence. But, it is free glutamate that is the culprit. Bound glutamate, found naturally in foods, is less dangerous because it is slowly broken down and absorbed by the gut so that it can be utilised by the tissues, especially muscle, before toxic concentrations can build up. Therefore, a whole tomato is safer than a puréed tomato. The only exception to this as stated, based on present knowledge, is in the case of ALS. Also, the tomato plant contains several powerful antioxidants known to block glutamate toxicity.[13]

Hydrolysed vegetable protein is a common food additive and may contain at least two excitotoxins: glutamate and cysteic acid. Hydrolysed vegetable protein is made by a chemical process that breaks down the vegetable's protein structure purposefully to free the glutamate as well as aspartate, another excitotoxin. This brown, powdery substance is used to enhance the flavour of foods, especially meat dishes, soups and sauces. Despite the fact that some health food manufacturers have attempted to sell the idea that this flavour enhancer is "all natural" and "safe" because it is made from vegetables, it is not. It is the same substance added to processed foods. Experimentally, one can produce the same brain lesions using hydrolysed vegetable protein as by using MSG or aspartate.[14]

A growing number of excitotoxins are being discovered, including several that are found naturally. For example, L-cysteine is a very powerful excitotoxin. It is now added to certain bread doughs and is sold in health food stores as a supplement. Homocysteine, a metabolic derivative, is also an excitotoxin.[15] Interestingly, elevated blood levels of homocysteine were recently shown to be a major, if not *the* major, indicator of cardiovascular disease and stroke. Equally interesting is the finding that elevated levels of homocysteine are also implicated in neurodevelopmental disorders, especially anencephaly and spinal dysraphism (neural tube defects).[16] (It is thought that there is a protective mechanism of action associated with the use of the prenatal vitamins B12, B6 and folate when used in combination.) It remains to be seen if the toxic effect is excitatory or due to some other mechanism. If it is excitatory, then unborn infants would be endangered as well by glutamate, aspartate (part of the aspartame molecule) and the other excitotoxins. Recently, several studies found that all Alzheimer's patients examined had elevated levels of homocysteine.[17]

One interesting study found that persons affected by Alzheimer's disease also have widespread destruction of their retinal ganglion cells.[18] Interestingly, this is the area found to be affected when Lucas and Newhouse discovered the excitotoxicity of MSG. While this does not prove that dietary glutamate and other excitotoxins cause or aggravate Alzheimer's disease, it is powerful circumstantial evidence. When all of the information known concerning excitatory food additives is analysed, it is hard to justify continued approval by the FDA for the widespread use of these additives.

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THE EFFECTS OF TOXIC FREE RADICALS

It is interesting to note that many of the same neurological diseases associated with excitotoxic injury are also associated with accumulations of toxic free radicals and destructive lipid oxidation products.[19] For example, the brains of Alzheimer's disease patients have been found to contain high concentrations of lipid peroxidation products and evidence of free radical accumulation and damage.[20, 21, 22]

In the case of Parkinson's disease, we know that one of the early changes is the loss of one of the primary antioxidant defence systems, glutathione, from the neurons of the striate system and especially in the substantia nigra.[23] It is this nucleus that is primarily affected in this disorder. Accompanying this, is an accumulation of free iron, which is one of the most powerful free radical generators known.[24] One of the highest concentrations of iron in the body is within the globus pallidus and the substantia nigra. The neurons within the latter are especially vulnerable to oxidant stress because the catabolic metabolism of the transmitter, dopamine, can proceed to the creation of very powerful free radicals; that is, it can auto-oxidise to peroxide, which is normally detoxified by glutathione. As we have seen, glutathione loss in the substantia nigra is one of the earliest deficiencies seen in Parkinson's disease. In the presence of high concentrations of free

iron, the peroxide is converted into the dangerous and very powerful free radical, hydroxide. As the hydroxide radical diffuses throughout the cell, destruction of the lipid components of the cell takes place—a process called "lipid peroxidation". Of equal importance is the generation of the powerful peroxynitrite radical, which has been shown to produce serious injury in cellular proteins and DNA, both mitochondrial and nuclear.[25]

Using a laser microprobe mass analyser, researchers discovered that iron accumulation in Parkinson's disease is primarily localised in the neuromelanin granules (which gives the nucleus its black colour).[26] Other studies showed that there is dramatic accumulation of aluminium within these granules.[27] Most likely, the aluminium displaces the bound iron, releasing highly reactive free iron. It is known that even low concentrations of aluminium salts can enhance iron-induced lipid peroxidation by almost an order of magnitude. Further, direct infusion of iron into the substantia nigra nucleus in rodents can induce a parkinsonian syndrome and a dose-related decline in dopamine. Recent studies indicate that individuals having Parkinson's disease also have defective iron metabolism.[28]

Another early finding in Parkinson's disease is the reduction in complex I enzymes within the mitochondria of this nucleus.[29] It is well known that the complex I enzymes are particularly sensitive to free radical injury. These enzymes are critical to the production of cellular energy. As we shall see, when cellular energy is decreased, the toxic effect of excitatory amino acids increases dramatically.

In the case of ALS, there is growing evidence that similar free radical damage, most likely triggered by toxic concentrations of excitotoxins, plays a major role in the disorder.[30] Several studies demonstrated lipid peroxidation product accumulation within the spinal cords of ALS victims, as well as iron accumulation.[31]

It is now known that glutamate acts on its receptor via a nitric oxide mechanism.[32] Overstimulation of the glutamate receptor can produce an accumulation of reactive nitrogen species, resulting in the generation of several species of dangerous free radicals, including peroxynitrite. There is growing evidence that, at least in part, this is how excess glutamate damages nerve cells.[33] In a multitude of studies, a close link was demonstrated between excitotoxicity and free radical generation.[34–37]

Other studies showed that certain free radical scavengers (antioxidants) successfully block excitotoxic destruction of neurons. For example, vitamin E is known to block glutamate toxicity completely *in vitro*.[38] Whether it is as efficient *in vivo* is not known. But it is interesting in the light of recent observations that vitamin E, combined with other antioxidant vitamins, slows the course of Alzheimer's disease and is suggested to reduce the rate of advance in a subgroup Parkinson's disease as well.

In the Datatop study of the effect of alpha-tocopherol alone, no reduction in disease progression was seen. The problem with this study was the low dose that was used and the fact that the DL-alpha-tocopherol used is known to have a much lower antioxidant potency than D-alpha-tocopherol. Stanley Fahn found that a combination of D-alpha-tocopherol and ascorbic acid in high doses reduced progression of the disease by 2.5 years.[39] Tocotrienol may have even greater benefits, especially when used in combination with other antioxidants. There is some clinical evidence, including my own observations, that vitamin E, especially in the form of D-alpha-tocopherol, also slows the course of ALS. I would caution that antioxidants work best in combination, and that when used separately can have opposite, harmful effects. That is, when antioxidants, such as ascorbic acid and alpha-tocopherol, become oxidised themselves—such as in the case of dehydroascorbic acid—they no longer protect, but rather act as free radicals themselves. The same is true of alpha-tocopherol.[40]

Again, it should be realised that excessive glutamate stimulation triggers a chain of events that in turn sparks the generation of large numbers of free radical species, both as nitrogen and oxygen. These free radicals have been shown to damage cellular proteins (protein carbonyl products) and DNA. The most immediate DNA damage is to the mitochondrial DNA, which controls protein expression within that particular cell and its progeny, producing rather profound changes in cellular energy production. It is suspected that at least some of the neurodegenerative diseases, Parkinson's disease in particular, are affected in this way.[41] Chronic free radical accumulation would result in an impaired functional reserve of antioxidant vitamins, minerals, enzymes and thiol compounds necessary for neural protection. Chronic unrelieved stress, chronic infection, free-radical-generating metals and toxins, and impaired DNA repair enzymes all add to this damage.

What has been shown in all these studies is a direct connection between excitotoxicity and free radical generation in a multitude of diseases and disorders such as seizures, strokes, brain trauma, viral infections and neurodegenerative diseases.

We know there are four main endogenous sources of oxidants:

1. Those produced naturally from aerobic metabolism of glucose.
2. Those produced during phagocytic cell attack on bacteria, viruses and parasites, especially with chronic infections.
3. Those produced during the degradation of fatty acids and other molecules that produce H_3O_2 as a by-product. (This is important in stress, which has been shown to increase brain levels of free radicals significantly.)
4. Oxidants produced during the course of p450 degradation of natural toxins. And, as we have seen, one of the major endogenous sources of free radicals is from the exposure of tissues to free iron, especially in the presence of ascorbate. Unfortunately, iron is one mineral heavily promoted by the health industry, and is frequently added to many foods, especially breads and pastas. Copper is also a powerful free radical generator and has been shown to be elevated within the substantia nigra of parkinsonian brains.[42]

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Interestingly, free radicals were shown to prevent glutamate

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uptake by astrocytes as well, which would significantly increase extracellular glutamate levels.[43] This creates a vicious cycle that will multiply any resulting damage and malfunctioning of neurophysiological systems, such as plasticity.

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